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ARTICLE

Pharmacogenetic testing in primary care could bolster depression treatment: A value proposition

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Abstract

Pharmacogenetic testing could reduce the time to identify a safe and effective medication for depression; however, it is underutilized in practice. Major depression constitutes the most common mental disorder in the US, and while antidepressant therapy can help, the current trial –and error approach can require patients to endure multiple medication trials before finding one that is effective. Tailoring the fit of pharmacogenetic testing with prescribers' needs across a variety of settings could help to establish a generalizable value proposition to improve likelihood of adoption. We conducted a study to explore the value proposition for health systems using pharmacogenetic testing for mental health medications through prescribers' real-world experiences using implementation science concepts and systematic interviews with prescribers and administrators from four health care systems. To identify a value proposition, we organized the themes according to the Triple Aim framework, a leading framework for health care policy which asserts that high-value care should focus on three key metrics: (1) better health care quality and (2) population-level outcomes with (3) reduced per capita costs. Primary care providers whom we interviewed said that they value pharmacogenetic testing because it would provide more information about medications that they can prescribe, expanding their ability to identify medications that best-fit patients and reducing their reliance on referrals to specialists; they said that this capacity would help meet patients' needs for access to mental health care through primary care. At the same time, prescribers expressed differing views about how pharmacogenetic testing can help with quality of care and whether their views about out-of-pocket cost would prevent them from offering it. Thus, implementation should focus on integrating pharmacogenetic testing into primary care and using strategies to support prescribers' interactions with patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Pharmacogenetic testing (PGx)can indicate how patients may respond to medications for mental health care, shortening time to effectiveness and decreasing likelihood of side effects. However, prescribers do not widely use it in practice. Variability in beliefs (about clinical utility and ability), guidelines, and coverage hinder use.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study explored the question of value from a healthcare system perspective of using pharmacogenetic testing for prescribing mental health medications.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Our findings indicate that pharmacogenetic testing could help to improve access to mental health care through additional tools and training for primary care providers to support the use of pharmacogenetic testing. However, primary care providers differed from others in their views about the benefit of incorporating pharmacogenetic testing into their practice. Primary care providers indicated that they would value pharmacogenetic testing as a tool to expand their ability to treat patients with mental health needs by increasing their own capacity to identify the best-fit medications in less trial time. To improve the likelihood of adoption, health care systems could focus on investing in primary care with strategies to increase primary care prescribers' familiarity with both psychiatric care and genetic testing. To our knowledge, no other research study has focused on using a combined bottom-up and top-down approach (through eliciting providers' real-world experiences and organizing findings according to the policy-focused Triple Aim framework) to develop a value proposition for using pharmacogenetic testing with antidepressant prescribing.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Focusing implementation of pharmacogenetic testing for mental health medication prescribing in primary care could help to close a gap between discovery and uptake. Understanding prescribers' views can help focus implementation strategies to advance pharmacogenetic testing into practice. Programs can be in place with tests available to order; however, if providers do not order or use results low use of pharmacogenetic tests will remain.

INTRODUCTION

Major depression, the most common mental health disorder in the United States, affected approximately one out of 10 Americans in 2020.[1] While antidepressant therapy is effective, the current "trial and error" treatment approach can require patients to endure multiple medication trials before finding one that is effective, a time during which patients' symptoms may worsen and trust wane.[2] Testing for genes known to impact drug metabolism and activation, known as pharmacogenetic testing, can indicate how individuals may respond to a medication with respect to medication efficacy and risk of side effects. To better prescribe the right medication for the right patient at the right time, prescribers should consider patients' genetic and clinical factors, reports of symptoms, and their experiences with treatment.[3]

The Clinical Pharmacogenomics Implementation Consortium (CPIC), an international consortium that systematically curates and translates evidence on pharmacogenetics into recommendations of how to use pharmacogenetic test results has developed guidelines for three pharmacogenes, CYP2D6, CYP2B6, and CYP2C19, that are associated with metabolism of selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).[4] In addition, the US Food and Drug Administration (FDA) has updated package inserts to include information about pharmacogenes for several

psychiatric drugs.[5] Clinical trials have started to demonstrate improved depression response and remission rates with the use of genotype-guided prescribing as compared with usual care.[6] While the question of cost–benefit of testing depends largely on the current cost and outcomes of treatment based on testing, studies have indicated cost-effectiveness or cost savings from a system or payer perspective[7]; we can expect coverage to increase in the future making price less of a factor.[8]

However, realizing benefits from pharmacogenetic testing in real-world practice will depend on the extent to which prescribers value and use it.[9] Several implementation studies on pharmacogenetic testing have been conducted,[8,10–15] and some specifically for psychiatric medications.[16–20] While prescribers have begun to use pharmacogenetic testing in routine care in different specialties, widespread adoption has lagged both across and within institutions: analysis of administrative claims for Medicare and Medicaid in one US state found that only 4.4% of Medicaid beneficiaries and 10.5% of Medicare beneficiaries who had begun a prescription of a medication included in the FDA table of drugs with pharmacogenetic testing information on the label actually received pharmacogenetic testing.[21] Prior work has shown that a multitude of factors, from individual prescriber to larger structural issues, are barriers to pharmacogenetic testing adoption.[17,38] On an individual level, prescribers vary in their beliefs about the clinical utility of pharmacogenetic testing and in their own ability to effectively use the test results in practice.[15,22–24] Additionally, unclear or inconsistent professional guidelines and coverage policies complicate prescribers' decisions about whether to use pharmacogenetic testing in their practice.

While much of the literature has focused on reasons that prescribers have not adopted pharmacogenetics, less attention has focused on exploring facilitators for adopting testing. Knowledge about adoption facilitators at the prescriber and system levels would help to better characterize pharmacogenetic testing's value proposition, that is, how it can uniquely meet the needs to improve care. According to the International Society for Pharmacoeconomics and Outcome Research (ISPOR) Precision Medicine Special Interest Group, prescribers value having the "best evidence-based practice" that includes information to help make the most accurate and confident decisions for better, safer outcomes; system leaders also value high-quality care, as well as managing the health system's finances and reputation.[25] Sibalija et al. (2021) developed a value proposition for pharmacogenetic testing specifically by interviewing prescribers in a precision medicine clinic about aspects of their jobs (tasks), pains (challenges), and gains (benefits) that affected their decision to use pharmacogenetic testing; they developed standard value propositions for that specific clinic setting and targeted value propositions for specific treatments (e.g., cancer).[26] Articulating the fit of pharmacogenetic testing with prescribers' needs across a variety of settings could help to establish a generalizable value proposition to improve the likelihood of adoption on a wider scale.[27]

We conducted a study to explore the value proposition for health systems using pharmacogenetic testing for mental health medications based on prescribers' real-world experiences. Specifically, we elicited data and identified themes using concepts relevant to the implementation of high-value care from health services research and policy frameworks. These data will provide a specific use case to the work initiated by ISPOR, which can help health systems understand why and how pharmacogenetic testing can add value to mental health care practice.

METHODS

We conducted semi-structured interviews from April 2022–December 2022 with two groups: (1) healthcare providers at four institutions who prescribed mental health medications to understand reasons for use (or not) of pharmacogenetic tests in their practice; and (2) administrators at the same health care institutions to gather information about the prescribers' organizational contexts. Questions covered the following concepts from two implementation science frameworks—the Theoretical Domains Framework (TDF) and the Consolidated Framework for Implementation Research (CFIR): support, implementation climate, leadership engagement, available resources, ability (personal skills, procedural knowledge), benefits (beliefs about consequences and relative advantage), evidence strength and quality (belief in state of evidence on PGx for mental health), and whether they considered costs in their decision to use PGx testing in practice.[28-30] (See interview guides in Data S1 for questions by concept).

We used snowball sampling approaches to identify participants. We first conducted semi-structured interviews with collaborators at each institution to obtain background knowledge. The collaborators then referred the research team to a colleague in an administrative role who would also have knowledge about pharmacogenomic testing implementation at their institutions. The collaborators additionally introduced prescribers to the study coordinator by email, who then followed up to describe the project and invite them to participate. The interviews, conducted by Zoom, lasted ~30–45 min. We recorded and transcribed all the interviews. This study was approved by the Duke University IRB (#Pro00109184).

Two authors (NS and MR) reviewed the transcripts to identify themes through content analysis of the coded

data.[31] Discrepancies in identified themes were resolved via discussion with the larger team. To hone in on a value proposition, we organized the themes according to the Triple Aim framework, a leading framework for healthcare policy which asserts that high-value care should focus on three key metrics: (1) better healthcare quality and (2) population-level outcomes with (3) reduced per capita costs.[32]

RESULTS

Sample

The overall sample consisted of 37 individuals interviewed from four healthcare systems, including $n = 8$ admins (2 from each system) and 29 prescribers ($n = 4$–12 from each system). (See Table 1) Among the 29 prescribers, 16 were pharmacogenetic testing adopters (a prescriber who either ordered a test for CYP2C19 and CYP2D6 or used/disclosed results of a test automatically generated by their clinical institution) and 13 were non-adopters. Each health system was at a different stage of pharmacogenetic testing implementation: we describe these different contexts in Table 2 using the EPIS (Exploration, Preparation, Implementation, Sustainment) and CFIR frameworks.[30,33]

Findings

Themes from the prescriber interviews include statements about how pharmacogenetic testing affects the *quality* of prescribing ("The art of prescribing"), how it intersects with population health (Meeting patients' needs), and implications of *cost* (Considering patients' costs). Generally, we found that adopters consistently expressed positive sentiments, while non-adopters conveyed variability in their views. We describe the cross-cutting themes and identify distinct issues between adopting and non-adopting prescribers (Table 3).

Quality: Art of prescribing

Art of prescribing refers to the skill involved in determining the best course of action for each individual case. Prescribers must use their own judgment when prescribing, even with guidelines for dosing and treatment selection. Prescribers discussed how pharmacogenetic testing fits, or does not fit, with their own beliefs about and approaches to prescribing, including how they evaluated its relative advantage over the standard of care.

While prescribers generally suggested that pharmacogenetic testing does not offer a clear advantage above and beyond the current trial and error approach, they also commonly said that it enhances, or would enhance, their approaches, giving them more confidence and patient buy-in in the medication choices. One interviewee, an outpatient pediatrician who has used pharmacogenetic testing through an external lab for 5 years, said that testing had given them "confidence" in where to start or go with dosing.

> ... over the five years, I've had increased confidence. I also have a psychiatrist just colleague/friend at [Institution] that I've run some cases by just offline, and I feel like she's helped me gain confidence. Really, for me, I'm looking more than anything – it's at how it's metabolized in terms of how either quickly I'm comfortable ramping up medicines or how slowly I need to go based on metabolism... I also should say, as a pediatrician, I really stick to the very established SSRI's. Currently, I really only use Prozac, Lexapro, and Zoloft... So, even though the reports give, you know, 35 drugs, I'm really only looking at the three that I feel very comfortable using, and if it's outside the scope of those, that's when I will reach out to the psychiatrist. – provider from site 3
>
> (EPIS implementation stage)

Another primary care prescriber who had not used pharmacogenetic testing and worked in a setting that had not adopted pharmacogenetic testing echoed this sentiment of enhanced prescribing, explaining that they valued the scientific aspect of pharmacogenetic testing for their treatment decisions: "And being the medical world, we work in science. So, a lot of the decisions we make are based on research and evidence-based reviews and years of studying. So, if I had something more concrete, then I'm more comfortable with giving a certain medication or treatment plan." – provider from site 2 (EPIS preparation stage).

Prescribers also discussed how pharmacogenetic testing enhanced their practice by gaining buy-in from patients about diagnoses or treatment. A primary care prescriber from site 4, at the EPIS sustainment stage, described how they discussed test results with patients when considering treatment options, saying "... sometimes having more patient buy-in in something that also would be a reasonable choice gives, in my experience, a better outcome. A lot of times, the algorithms, you can kind of branch off and do one of two things. I would choose the

TABLE 1 Characteristics of pharmacogenetic testing contexts at four health care systems from April 2022–December 2022.

Concepts	Site 1	Site 2	Site 3	Site 4
Implementation stage[33]	Exploration	Preparation	Implementation	Sustainment
Implementation climate[29]	Pharmacy supportive of pharmacogenetic testing; however, competition from other strategic initiatives and unclear about where hospital leadership stands	Shared perception of the importance of pharmacogenetic testing within the pharmacy department; however not a system-wide practice	Program for ordering pharmacogenetic testing in place though not well promoted throughout the system. Pharmacogenetics has become "commonplace" and other priorities preventing updates	System provides a lot of support and demonstrates the value of pharmacogenetic testing (for example, a dedicated building in the main location, prior mandated clinician training, and dedicated resources like marketing support, research manager, and IT). Some challenges expanding to rural clinics with varied local support; are generally seen as urban rather than enterprise initiatives
Leadership engagement[29]	No formally appointed implementation leader, though pharmacist are interested and working on research initiatives as a collateral duty	Leader appointed 2 years prior by the Chief Pharmacy Officer through ambulatory care	Administrator (geneticist) leading it with support from others (nurse educator, clinical pharmacist with specialty in psychiatry, informaticist)	Group leadership model. Started with group of physicians and hired pharmacist to manage and molecular pathologist to bridge. The full committee meets every other month with lab staff to help make decisions. Physicians identifying internal medicine champions in each city
Available resources[29]	No institutionally supported resources are available	Informatics build available to order test and scan results into Electronic Health Record. Consult available via informatics build to ask pharmacist-specific questions. Piloting limited clinical decision support (e.g., does not include CYP2D6) based on discrete fields in record	Automatic orders for inpatient admission. However, prescribers can bypass. Clinical decision support available in the form of patient information handout that includes therapeutic recommendations available via website. Waiting for the EPIC genomics module to update to "more intelligent alerts"; however, need resources to continue to innovate, including protected staff time	Clinical decision support and in-house lab. System subsidizes to keep costs down. Specialists are available in clinics in each hub region to help prescribers interface with pharmacists or genetic counselors. One pharmacist works with IT. Number of pharmacists available to consult growing (from 3 (2 full-time equivalent) in 2018) to 6 (5 full-time equivalent) in 2022)

TABLE 2 Characteristics of prescribers ($N = 29$) interviewed about pharmacogenetic testing at four health care systems from April 2022-December 2022.

	Site 1	Site 2	Site 3	Site 4	Total
Adopters[a] (*n*)	2	1	3	10	16
Non-adopters (*n*)	2	7	2	2	13
"What clinical area do you work in primarily?" (*n*)					
Primary care	2	7	3	8	20
Psychiatry	0	1	2	4	7
Other[b]	2	0	0	0	2
"What is your primary location?" (*n*)					
Inpatient	1	0	1	0	2
Outpatient	3	8	4	12	27
Demographics					
"What is your age?" Mean (min, max)	51 (38,63)	36 (26,48)	47 (43,53)	46 (30,66)	44 (30,66)
Decline to answer (*n*)	0	2	0	1	3
"Gender: How do you identify?" (*n*)					
Man	2	2	3	6	13
Woman	2	5	2	6	15
Prefer to self-identify	0	0	0	0	0
Decline to answer	0	1	0	0	1
"Race/Ethnicity: How do you identify?" (*n*)					
American Indian or Alaska Native[c]	0	0	0	0	0
Asian[d]	1	0	0	0	1
Black or African American[e]	0	1	0	1	2
Hispanic or Latino[f]	0	0	0	0	0
Native Hawaiian or Other Pacific Islander[g]	0	0	0	0	0
White[h]	3	6	5	11	25
Prefer to self-identify	0	0	0	0	0
Decline to answer	0	1	0	0	1
"Have you been trained in how to use pharmacogenetic testing in your daily practice? Please tell me more." (*n* reporting some training (med school/residency/CME)	2	7	3	8	20

[a]A prescriber who either order a test for CYP2C19 and CYP2D6 or uses/discloses results of a test automatically generated by their clinical institution.

[b]Internal Medicine Psychiatry; a mix of Primary Care and Psychiatry.

[c]A person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment.

[d]A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam.

[e]A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

[f]A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

[g]A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[h]White. A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

one that the patient has, you know, that we've had a more informed-consent conversation about." Likewise, prescribers said that their "affluent" or younger patient populations tend to value having more information and want to be part of the solution. In general, however, prescribers said that they found it best to use pharmacogenetic testing for patients who receive prescriptions for the first time or do not respond to the initial treatment, because it can backfire if the results contradict the patient's own experience with the medication.

TABLE 3 Concepts, themes, and findings about a value proposition of pharmacogenetic testing in mental health care from individual interviews with $N = 29$ prescribers.

Concepts[32]	Themes	Findings
Quality	The Art of Prescribing Prescribers must use their own skill to determine the best course of action for each individual case.	No clear advantage of pharmacogenetic testing over the standard of care for adopters and non-adopters though improves confidence in prescribing; certain non-adopters expressed that pharmacogenetic testing would interfere with the relational aspect of prescribing
Population Health	Meeting Patients' Needs Pharmacogenetic testing can help meet population-level needs for mental health care.	Primary care prescribers discussed the advantage of reducing inequities in access to mental health care by using pharmacogenetic testing, while psychiatrists did not perceive the advantage
Cost	Considering patients' costs Adopting and non-adopting providers differentially considered test costs a barrier for testing patients	Although prescribers overall viewed pharmacogenetics as potentially saving costs from trial and error, certain adopters let patients decide willingness to pay, while non-adopters did not view the information as worth any out-of-pocket cost

Prescribers not willing to adopt pharmacogenetic testing expressed that they did not believe that it would provide a relative advantage or meet patients' needs and that it could potentially detract from "the art side" or relational prescribing. For example, one prescriber from site 1, at the EPIS exploration stage, who worked in inpatient psychiatry and internal medicine and served on their hospital's pharmacy and therapeutics committee, said that they did not believe that pharmacogenetic testing would help their patients due to the concern that patients may expect pharmacogenetic testing to help them find the "right" medication and reduce the benefit of "the one main tool we have in behavioral health, which is interpersonal connection and ... the art side...". A pediatric psychiatrist who had used pharmacogenetic tests in a previous position indicated that while they believed in the validity of the test results, they did not buy into the utility. This respondent, from site 2 at the EPIS implementation stage, found that test results can both mislead patients and overwhelm prescribers and therefore "the misunderstanding is greater than the potential for benefit and so I just don't bother." Furthermore, this respondent stated that "The results were very unfamiliar. It wasn't as clear to read... crazy and scary to me, so I just didn't bother." Another prescriber, a clinical pharmacist, said that they did not believe that pharmacogenetic testing would provide the right kind of information:

> Yeah, so I'll say with psychiatry and team management, we're really just treating symptoms of a problem. We're dosing medications based off what it states and how the patient feels. If they feel better or if they feel worse. And so, knowing the specifics of how the drug is metabolized is not really going to give us an indication from the research that I've seen, the evidence that we have on it. It's not going to give us information on how it's going to make the patient feel. – provider from site 2 (EPIS preparation stage)

Population health: Meeting patients' needs

Prescribers were asked in interviews to consider the utility of routine pharmacogenetic testing for mental health care. While there were no evident differences by pharmacogenetic testing adoption status, there were differences observed between primary care prescribers and psychiatrists. Primary care prescribers described how their use of pharmacogenetic testing for prescribing mental health medication could reduce inequities in their patients' access to mental health care, while psychiatrists pointed out limitations for their practice.

Primary care prescribers said that pharmacogenetic testing appealed to them because it provides additional information to inform therapeutic decision-making for mental health medications on their own. One primary care prescriber practicing in a primary care outpatient clinic in a rural area explained:

> Definitely, in my area we deal with a lot of mental health issues... it's widespread and we have a lack of psychiatrists. So, even though they would benefit from establishing with a psychiatrist to have further diagnosis and other treatment, a lot of times, they're stuck with just primary care to deal with this... Which makes it even more challenging. So, there's a huge demand, and it's very – it's difficult for everybody involved, and I think having that extra tool to streamline the process would – it would be life changing... I'm assuming if somebody has failed one or two medications, I could then order this test and say "Okay, I have a reason to recommend this other medication to you" and "Let's try that before we jump through hoops to try to get you in to see psychiatry." I try to reserve my psychiatry referrals for patients who truly have mood disorders or psychotic disorders because our psychiatry offices are just really backed up with referrals. So, it's not usually an option. – provider from site 2
>
> (EPIS preparation stage)

This respondent had not yet adopted pharmacogenetic testing because they did not know how to access it through the health system. Another respondent in the same system who also had not yet used pharmacogenetic tests suggested that the practice would influence patients' acceptance of and adherence to mental health care:

> I think it would help a lot because, like I said, a lot of the times patients have a hard time even admitting that they have a mental health disorder, right?... So, if I'm telling them that there's a test that's studied that can be given to them to see what they will do well on, I think they'll be more inclined to take that medication than to just say, "Oh, my family medicine doctor's going to give me this medicine that they think may work." They'll have more confidence in my ability to treat them, as well... sometimes patients have a hard time with the wait for psychiatry or the idea of seeing a psychiatrist. So, a lot of the time in family medicine, we are prescribing and managing their medication. – provider from site 2
>
> (EPIS preparation stage)

On the other hand, psychiatric prescribers pointed out limitations in the utility of pharmacogenetic testing for them; in their opinion, mental health care should focus on improving the precision of diagnoses rather than medications. One inpatient psychiatrist from a system that had a higher level of institutional support for pharmacogenetic testing suggested that information about how people metabolize medications from pharmacogenetic testing offers little benefit compared with having a more precise diagnosis:

> I think the future might be frankly even better in identifying subtypes of depression, per se, based on not your pharmaco- but your genetic profile and may help guide us even better...So, if we could identify subgroups of patients that maybe have a better response to a particular medicine based on their phenotype, frankly it might even be more helpful than blood levels... we call all sad people major depression when it's probably a heterogenous group of a lot of different pathways to depression. So, we're not dealing with a single entity, and it makes it very hard to study. – provider from site 4
>
> (EPIS sustainment stage)

Hospital-based psychiatrists also indicated that pharmacogenetic testing would offer little benefit for the patients they see, who have high needs. As one psychiatrist who worked primarily at an institution that automatically ordered pharmacogenetic tests upon admission said, "Unfortunately, just by the nature of the way psychiatrists practice these days, for someone who's an MD, often we're getting the sickest people... where you have many different medication failures before, whatever else, now they're on four different medications and so the impact of one medication is probably less important at that point." – provider from site 3 (EPIS implementation stage).

Two prescribers with combined internal medicine and psychiatric training and from the same health systems expressed different views from each other about priorities for using pharmacogenetic testing. One prescriber who worked in an inpatient setting and had not yet used pharmacogenetic testing suggested that the subjectivity required to diagnose depression and other mental health disorders posed a greater risk to patients than the time required to trial common depression medications:

> I don't see that the benefits are there compared to the costs of the trial and error. You obviously wouldn't trial and error with a potentially lethal chemotherapy medication. I think it's reasonable to trial and error with a medication that you're comfortable with having. Because the first thing you have to do is diagnose the illness. And again, we don't have blood tests for depression, or bipolar disorder, or schizophrenia. We have clinical evaluations and clinical impressions. You have symptoms and that's what we have. Which is, again, different from a biopsy to prove cancer...So, I think psychiatry needs to work on the diagnostic issues before jumping whole hog into genotype testing. – provider from site 1
>
> (EPIS exploration stage)

The other prescriber who worked in an outpatient setting described testing as advantageous for population health access to mental health care.

> Well, I think one of the ways that it could help if you're really looking at a population level is we know that access to mental health services is sparse, to say the best. So, if we could institute a way to kind of get to efficacy sooner, thereby limit the burden on mental health services in that sense, that could be really helpful from a population standpoint. – provider from site 1
>
> (EPIS exploration stage)

This prescriber started using pharmacogenetic tests after learning about it at an American Psychological Association conference and, around the same time, attended an in-service presentation. Because their health system, situated in an urban setting, did not have a standard process for ordering pharmacogenetic tests, this prescriber had used an external lab. They indicated that they used pharmacogenetic tests selectively when a patient might have exhibited intolerance or failed efficacy to a couple of medications.

Cost: Considering patients' costs

Although prescribers generally noted that pharmacogenetic testing could reduce overall healthcare costs, adopters and non-adopters differed as to whether the cost of the test prevented them from offering it.

Certain adopters indicated that test costs did not pose a barrier. Instead, they let patients decide according to their willingness to pay. One primary care prescriber who worked in a rural outpatient setting described how they presented test cost to patients:

> ...in our area there is, it's not poverty, but ... we're caught with these extra costs, like a patient wants to know what it's going to do to help... Like you're running through different kinds of meds, it's not working...And then I'll mention the [test] cost for them [the patients] and then because that will dictate if they'll even entertain it. So, if they're agreeable to a potential cost, then I usually refer...So, I'm usually like maybe it's a better path to use the genetic testing so you can maybe pick a medicine that works a little bit better for you. And that's where I would go with it, especially if there's a cost associated. – provider from site 2
>
> (EPIS preparation stage)

In another outpatient setting, a pediatrician who used an external lab said that they explained the cost of testing, which has a sliding scale and a maximum price, to parents. "So, the way that [external lab] testing currently works is they guarantee they will not charge families more than $330.00 per test if their insurance doesn't pay, and it's a sliding scale. So, I discuss that cost but really allow the parents to decide. So, I don't decide to offer it or not offer it based on parents' payment...my ...perception of payment...I explain it, but I don't not offer." – provider from site 3 (EPIS implementation stage) Respondents from a health system that had subsidized the cost to patients indicated that they did not necessarily rely on the coverage as a selling point. One psychiatrist said that while they generally do not keep track of test costs, they believed that the clinical evidence itself justified using pharmacogenetic tests:

> ...Currently, I think it's clear enough to justify it... I'm trying to be judicious about my patient's welfare and their means, and I'm not trying to just do a test because we can. I don't want to do the test unless it's going to give me some actionable information. As I follow literature, which I obviously do not follow all that closely, it's kind of gone up and down in terms of how useful it is. And, right now, I feel like it's coming back to a point that it's more useful...I'm looking at a patient who's struggling, has been on a bunch of stuff, and I'm just looking for any sort of rational, logical basis to direct my treatment...This is one of the points that the ... paper makes is that by doing this and getting the testing, they were

> able to save costs... It was enough to tip me back in the direction of ordering. – provider from site 4
>
> (EPIS sustainment stage)

In contrast, non-adopters from different systems who did not offer the test as an option to patients indicated that they did not perceive value or have enough knowledge and thus did not find the resultant information worth the out-of-pocket cost to patients:

> I recognize that there are certain medications that do require knowledge of the metabolism, but for most of these medications they are not narrow therapeutic index medications. We don't know enough of the nuances behind the mechanism to even determine does a 10 percent difference in metabolism matter for what will affect the patient. Most of my patients [who have obtained pharmacogenetic testing] say they spent about $200.00 to get the results, so... with the information that it gives us, that is a large burden. A lot of my patients are lower socioeconomic standing... – provider from site 2
>
> (EPIS exploration stage)

Other respondents said that not knowing about costs prevented them from offering it. For example, a medical director of an outpatient primary care group from site 1 (EPIS exploration stage) that had attempted to incorporate pharmacogenetic testing into their practice said, "There's always uncertainty about insurance coverage... Yeah, that was an issue, and I'm not sure how third-party payers pay for this." A pediatrician who works in a system that requires opting out of ordering pharmacogenetic tests bridged both sentiments, saying that while they have limited knowledge about pharmacogenetic testing, they do not believe that the information provides any advantage over their routine clinical practice and thus, the cost of testing is not supported:

> I feel like the results that I've seen are kind of nebulous, and it sort of tells me, "Oh, this person's a little bit higher metabolizer; this is a slower metabolizer... And then, I'm still going to start with a few medicines that I know and have a lot of clinical experience with ... There's probably about three medicines that we use a lot for anxiety and depression in first line in pediatrics, right? No, I mean, because I'm going to probably start fairly low and then I titrate up versus not. So ... I don't feel like it's going to really impact whether I'm going to start low and kind of titrate up. The cost feels unnecessary... I have no idea how much it costs. I mean, for all transparency. I don't know...But if it's a test that I'm not going to really use to change clinical decision-making, all cost is too high, right? – provider from site 3
>
> (EPIS implementation stage)

DISCUSSION

Our findings suggest that a key value proposition of pharmacogenetic testing is that it could help meet patients' needs for access to mental health care through primary care. At the same time, prescribers expressed differing views about how pharmacogenetic testing can help with quality of care and whether their views about out-of-pocket costs would prevent them from offering it. Thus, implementation could focus on integrating pharmacogenetic testing into primary care and using strategies to support prescribers' interactions with patients.

Primary care prescribers in this study said that they want the capability that they believe pharmacogenetic testing could offer. Primary care prescribers already treat a substantial number of patients who have mental health care needs. In 2018, mental health constituted a concern in 16% of primary care visits, a 50% increase from 2006.[34] Additionally primary care clinicians prescribe most psychiatric medications for older adults with serious mental illness, particularly in rural areas.[35] One study found that privately insured individuals with serious psychological distress were more likely to obtain mental health care from a primary care provider and that primary care providers can help to meet their needs in the short term. Additionally, collaboration between primary and specialty care constitutes an important and effective aspect of health care transformation to value-based models.[36] However, systems need to invest in educating primary care prescribers: Huo et al. (2023) found that antidepressant prescriptions by primary care prescribers increased after receiving psychiatric training, supporting the idea that primary care prescribers could expand their reach of patients who may benefit from mental health medication.[37,38] Prior research also found support for primary care as a target for pharmacogenetics implementation in general, with favorable attitudes by providers and patients and the need for more supportive resources.[22,39] This study adds to this literature by identifying a value proposition for mental health care specifically.[22,39] However, this study design focused on comparison by adoption status rather than a clinical area; future research design

should focus on understanding more about the value of primary care by including more primary care providers in the sample.

Results do not point to a clear value proposition for prescribers from a care quality or patient cost perspective; however, these findings add to the literature by showing that prescriber comfort with or willingness to have discussions with patients would be important for test adoption. Prescribers expressed on the one hand concern that pharmacogenetic testing could take away from a relationship aspect of prescribing and on the other hand hope that it could provide an opportunity to facilitate patient buy-in. Future work should explore how inpatient versus outpatient setting affects these sentiments. One general strategy to facilitate prescribers' comfort with using pharmacogenetic testing is experiencing testing themselves.[40] Guidelines could be improved to direct providers on not only how to use results but also when to test and for whom.

AUTHOR CONTRIBUTIONS

N.R.S., M.C.R., L.B., D.C., S.B.H., R.R.W., B.K., N.J.P., L.R., and R.U. wrote the manuscript. N.R.S., D.C., S.B.H., R.R.W., N.J.P., L.R., and R.U. designed the research. N.R.S. and S.G. performed the research. N.R.S., M.C.R., L.B., D.C., S.B.H., R.R.W., and C.O. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

Dr. Wu is employed by 23andMe. She is a co-founder and shareholder of MeTree&You. Neither organization supported her effort, contributed, or benefited in any way from the research contained in this manuscript. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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